

REMARKS

Claims 1-3 remain pending in the above-identified application and stand ready for further action on the merits. Favorable action on the merits is earnestly solicited at present.

Information Disclosure Statement (IDS)

The Examiner states that WO 00/50395 A1, WO 02/36117 A1, and WO 02/059092 A1 listed on the IDS filed March 9, 2006 have not been received.

The undersigned has personally viewed documents on the USPTO PAIR website for the instant application and has verified that each of the above documents is part of the image file wrapper of the instant application. Any contentions of the USPTO to the contrary are erroneous.

For example, WO 00/50395 A1, WO 02/36117 A1, and WO 02/059092 are each listed in USPTO PAIR as having a Mailroom Date of 03-09-2006, each have a 371P Document Code, and their respective page counts are given as 45, 51 and 30.

Please also note that in the IDS filed March 9, 2006, it was expressly stated that WO 00/50395 A1, which is cited on page 1 of the specification and U.S. Patent Publication 2002-128480-A1 both correspond to JP-A-2000-247949; and that U.S. Patent Publication 2003-215523-A1 corresponds to WO 02/36117 A1. As such, the Examiner has already considered substantial equivalents of each of the WO 00/50395 A1 and WO 02/36117 A1 references. Additionally, the Examiner also cited the remaining WO 02/059092 reference in the PTO-892 form that accompanied the outstanding office action.

Accordingly, the Examiner is respectfully requested to initial the enclosed copy of the earlier submitted SB08 form to clearly indicate that the WO 00/50395 A1 and WO 02/36117 A1 references submitted with the IDS filed March 9, 2006 have been fully considered.

Priority Documents

The USPTO indicates that applicant has not filed a certified copy of foreign priority document JP 2003-318974.

However, The WIPO online Database indicates that the priority document 2003-318974 was submitted to WIPO and **Form PCT/IB/304** indicating Notification Concerning Submission or Transmittal of Priority Document was issued and a copy of the **Form PCT/IB/304** is present in the USPTO PAIR image file wrapper of the instant application (*i.e.*, it is listed in USPTO PAIR with a Mailroom Date of 03-09-2006, has a “371P” Document Code, and a page count of 1).

More precisely, PCT/IB/304 issued in the matter of PCT/JP2004/012650 (*from which the instant application is a 35 USC § 371 national phase application*) clearly indicating that on 15 October 2004 a copy of priority document JP 2003-318974 was received by the International Bureau under PCT Rule 17.1(a) or (b).

Accordingly, a copy of the JP 2003-318974 priority document should have been forwarded to the PCT branch of the USPTO from the International Bureau of WIPO and/or obtained by the PCT branch of the USPTO from the International Bureau of WIPO upon commencement of prosecution of the instant 35 USC § 371 application.

Accordingly, the USPTO is respectfully requested to obtain a copy of the JP 2003-318974 priority document from the International Bureau of WIPO, thereby fulfilling the requirements of 35 USC § 119(b).

Claim Rejections under 35 U.S.C. § 103(a)

Claims 1-3 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Haneda et al. (US 2002/0128480) in view of Owa et al. (*Bioorganic and Medicinal Chemistry Letters* 12 (2002) 2097-2100) and Crassier et al. (WO 02/059092) further in view of <http://en.wikipedia.org/wiki/Tetrahydrofuran>.

Legal Standard for Determining Prima Facie Obviousness

MPEP § 2141 sets forth the guidelines in determining obviousness. First, the Examiner has to take into account the factual inquiries set forth in *Graham v. John Deere*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966), which has provided the controlling framework for an obviousness analysis. The four *Graham* factors are:

- (a) determining the scope and content of the prior art;
- (b) ascertaining the differences between the prior art and the claims in issue;
- (c) resolving the level of ordinary skill in the pertinent art; and
- (d) evaluating any evidence of secondary considerations.

Graham v. John Deere, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966).

Second, the Examiner has to provide some rationale for determining obviousness. MPEP § 2143 sets forth some rationales that were established in the recent decision of *KSR*

International Co. v Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007). Exemplary rationales that may support a conclusion of obviousness include:

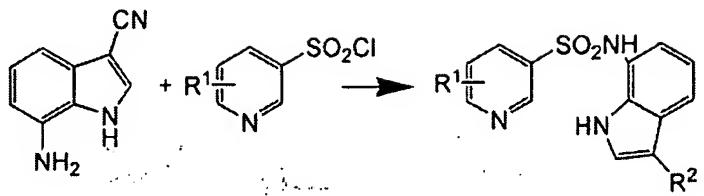
- (a) combining prior art elements according to known methods to yield predictable results;
- (b) simple substitution of one known element for another to obtain predictable results;
- (c) use of known technique to improve similar devices (methods, or products) in the same way;
- (d) applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;
- (e) "obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success
- (f) known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;
- (g) some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

As the MPEP directs, all claim limitations must be considered in view of the cited prior art in order to establish a *prima facie* case of obviousness. See MPEP § 2143.03.

Distinctions Over the Cited Art

Owa et al.

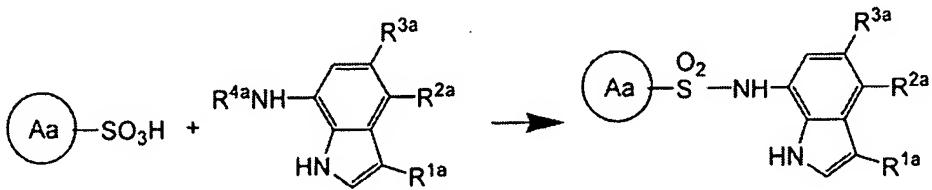
Owa et al. discloses the following reaction:



The solvent is ethyl acetate and the base is pyridine. However, Owa et al. never teaches or suggests that the above reaction can be carried out in a mixed solvent of water and C₁₋₆ alkyl acetate.

Haneda et al.

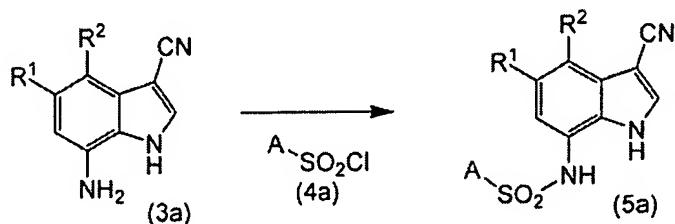
Haneda et al. discloses the following reaction (see paragraphs [0017]-[0019]):



According to paragraph [0020], “*Although there is no particular limitation for the solvent used for the reaction, those which dissolve the material substances and do not readily react with them are preferred. For example, pyridine, tetrahydrofuran, dioxane, benzene, ethyl ether, dichloromethane, dimethylformamide and a mixed solvent consisting of two or more which are selected from them can be used. In addition, when an acid is liberated with a progress of the reaction as in the case of using a sulfonyl halide in the reaction, it is preferred to conduct the reaction in the presence of an appropriate deacidifying agent and, therefore, the use of a basic solvent such as pyridine is particularly appropriate. When a neutral solvent is used, a basic substance such as an alkali carbonate or an organic tertiary amine may be added. Of course, the solvent which can be used is not limited to those listed here.*

The above reaction is carried out in THF in the presence of pyridine in Examples 1-7 and the above reaction is carried out in pyridine in Examples 9-10. Thus, **Haneda et al.** never teaches or suggests that the above reaction can be carried out in a mixed solvent of water and C₁₋₆ alkyl acetate.

On the other hand, the present invention uses a mixed solvent of water and C₁₋₆ alkyl acetate as the solvent for the following reaction:



As described in paragraph [0009] of the present specification, the advantages of using a mixed solvent of water and C₁₋₆ alkyl acetate are (1) safety of the concentration procedure is assured, (2) precipitation of the product is avoided, and (3) the total amount during extraction can be reduced since the reaction solvent also serves as the extraction solvent.

It was known in the art at the time of the priority date that THF tends to form peroxides. But, both of **Owa et al.** and **Haneda et al.** never teach or suggest water or a mixed solvent of water and an organic solvent; therefore those skilled in the art would never be motivated to use a mixed solvent of water and C₁₋₆ alkyl acetate to carry out the reaction in a solvent other than THF. Similarly, no reason or rationale is provided to those of ordinary skill in the art by **Owa et al.** or **Haneda et al.** to use a mixed solvent of water and C₁₋₆ alkyl acetate to carry out the reaction in a solvent other than THF.

Reference Examples 1A to 4A in the present specification (*see paragraphs [0047] to [0063]*) correspond to the synthesis disclosed in **Haneda et al.** The present specification compares the method of the present invention with the method in **Haneda et al.** (*see paragraphs [0064] to [0070]*). As is clear from paragraphs [0067] to [0070], the present invention can carry out the reaction more efficiently than the method disclosed in **Haneda et al.**

Crassier et al.

Crassier et al. discloses that steps (1) to (3), i.e. formylation, conversion of formyl to oxime and cyanation, are carried out in a one-pot process and the one-pot process gives better yields compared with the stepwise synthesis. But this is not true. Examples 1.1 to 1.3 of **Crassier et al.** provide a stepwise synthesis of methyl 3-cyanoindole-7-carboxlyate and Example 2.1 is a one-pot synthesis of the same compound. The yields of Examples 1.1 to 1.3 are 89.9% (*see page 19, line 6*), 95.0%^{*1} and 98.1%^{*2}, respectively.¹ The total yield of Examples 1.1 through 1.3 is $89.9\% \times 95.0\% \times 98.1\% = 83.8\%$. On the other hand, the yield of Example 2.1 is 48.9% (*see page 21, line 16*). The yield by one-pot synthesis is remarkably lower than that by stepwise synthesis. Those skilled in the art would never carry out one-pot synthesis in order to

¹*1 and ^{*2}:

Molecular weights of methyl 3-formylinole-7-carboxylate ($C_{11}H_9NO_3$), methyl 3-(hydroxyiminomethyl)indole-7-carboxylate ($C_{11}H_{10}N_2O_3$) and methyl 3-cyanoindole-7-carboxylate ($C_{11}H_8N_2O_2$) are 203.20, 218.21 and 200.20, respectively.

The yield of Example 1.2 is $(5.1/218.21)/(5/203.20)*100 = 95.0\%$

The yield of Example 1.3 is $(4.5/200.20)/(5/218.21)*100 = 98.1\%$

improve the yield. Crassier et al. actually teaches away from a one-pot synthesis.

In contrast, with regard to the instant invention, paragraphs [0064] to [0065] of the specification compare the yields of a stepwise synthesis and a one-pot synthesis of 3-cyano-4-methyl-7-nitro-1H-indole. The total yield of the stepwise synthesis is 85.8% and the yield of the one-pot synthesis is 97.6%. Thus the yield by the one-pot synthesis of the present invention is much higher than that by the stepwise synthesis of Haneda et al.

Based on such considerations, it is submitted that the cited art of record is incapable of providing those of ordinary skill in the art with any motivation, or reason or rationale for arriving at the instant invention as claimed. Any contentions of the USPTO to the contrary must be reconsidered at present, as they are not sustainable.

Conclusion

Based on the remarks presented herein, the USPTO is respectfully requested to issue a Notice of Allowance in the matter of the instant application clearly indicating that each of instantly pending claims 1-3 are allowed and patentable under the provisions of Title 35 of the United States Code.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact John W. Bailey, Reg. No. 32,881 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

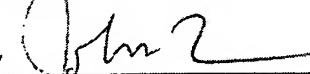
Application No. 10/571,285
Amendment dated January 9, 2009
Reply to Office Action of September 12, 2008

Docket No.: 1056-0134PUS1

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

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Attachment: Clean Copy of SB08 form originally filed with IDS on March 9, 2006